1. What is gadolinium and what is its use in clinical medicine?

   Gadolinium is a paramagnetic metal ion. Paramagnetic ions, such as gadolinium, tend to move into magnetic fields. This trait makes paramagnetic ions such as gadolinium useful for Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA). Gadolinium is approved for use with MRI as a contrast agent to provide a clearer picture of body organs and tissues. It is also used for MRA, another imaging procedure.

   Gadolinium-containing contrast agents are manufactured by a chelating process, a procedure in which large organic molecules form a stable complex around the gadolinium. The chelate reduces the chances of toxicity that could result from exposure to free gadolinium. This stable complex is eliminated via the kidneys in patients with normal functioning kidneys.

2. What is the difference between MRA and MRI?

   MRA is a special type of MRI used to study blood vessels. MRA is utilized to detect, diagnose and aid in the treatment of heart disorders, stroke, and vascular diseases.

3. Can an MRI and MRA be performed without gadolinium-containing contrast?

   MRI can be performed without contrast. However, gadolinium-containing contrast agents provide better diagnostic information in many instances as compared to MRI without contrast.

   The use of a gadolinium-containing contrast agent to enhance MRA is not FDA approved. MRA is able to provide detailed images of blood vessels without gadolinium-containing contrast. The use of gadolinium-containing contrast agents has been reported to enhance MRA.

4. Are there other approved MRI contrast agents that do not contain gadolinium?

   There are no other approved MRI contrast agents. Imaging contrast agents, such as iodinated contrast agents are used in Computed Tomography, plain X-ray and X-ray angiography. However, these iodinated contrast agents require X-ray imaging rather than MRI.

5. What is the concern regarding gadolinium-containing contrast agents?

   The information in the May 29, 2006, press release from the Danish Medicines Agency (DMA) and the January 2006 report by Grobner et al in Nephrology, Dialysis and Transplantation describe patients with renal failure who developed a rare, potentially life-threatening condition called Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy

(NSF/NFD). The DMA was concerned because all patients received a gadolinium enhanced MRA procedure a few weeks to a few months before developing NSF/NSD.

6. What is Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD)?

   NSF/NFD was first described in the medical literature in 2000. The first case of NSF/NFD was seen in 1997. The disease is seen in patients that have noticeably advanced renal failure. The disease causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. In addition, patients may experience fibrosis that has spread to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the interior areas of lung vessels. The clinical course of NSF/NFD is progressive and may be fatal.

7. What is the treatment for NSF/NFD?

   There is no consistently successful treatment for NSF/NFD.

   Improving renal function seems to slow or arrest NSF/NFD and may even result in a gradual reversal of NSF/NFD.

8. How many gadolinium-containing contrast agents has FDA approved? Was NSF/NFD seen with all of the U.S.-approved gadolinium-containing contrast agents?

   There are five FDA approved gadolinium-containing contrast agents (Omniscan®, OptiMARK®, Magnevist®, ProHance®, and MultiHance®).

   Omniscan® is the only approved gadolinium contrast agent in the countries where the Grobner report originated. FDA is actively investigating all gadolinium-containing contrast agents for any possible association with NSF/NFD.

9. Does the gadolinium-containing contrast agent (Omniscan®) cause NSF/NFD?

   Whether the gadolinium agent causes NSF/NFD is unknown. However, case reports from the DMA are of enough concern that FDA is further investigating a possible link between the condition and administration of gadolinium.

10. Why doesn't the FDA feel that the evidence for causality between gadolinium-containing contrast agents and the development of NSF/NFD is conclusive?

    The evidence associating the administration of a gadolinium-containing contrast agent to NSF/NFD is from case reports in patients with complicated medical histories. Concurrent medical illness and/or use of other medications may be a factor in the development of the condition. Further evaluation of these factors as well as use of gadolinium-containing contrast agents in patients with renal failure and in patients that develop NSF/NFD will be required.

11. What actions will FDA take regarding the new information about gadolinium-containing contrast agent administration and the development of NSF/NFD in patients with advanced renal disease?

    FDA is continuing to evaluate these reports, is undertaking discussions with experts in the field, will review results of previous and ongoing clinical trials with gadolinium-containing contrast agents, and is working with the manufacturers to review all safety reports and adverse event reports. FDA will assess all available information to determine if product labeling changes or other actions are necessary for gadolinium-containing contrast agents.

12. What information was known about serious side effects prior to the approval of gadolinium-containing contrast agents?

    The 5 U.S. approved gadolinium-containing contrast agents were approved between 1988 and 2004. In the combined pre-marketing studies for these approved gadolinium-containing contrast agents, over 3000 patients were studied.

    The most common serious side effect from gadolinium-containing contrast agents is an allergic reaction that is usually mild but can occasionally be severe and even result in fatalities. Some patients develop skin conditions, such as rash, sweating, itching, hives, and facial swelling. Most of these conditions are considered allergic in nature. Gadolinium-containing contrast agents can be very irritating to the veins into which injected, with superficial inflammation or irritation of blood vessels and blood clots.

    Very few patients with severely compromised kidney function or those on dialysis were studied in the pre-marketing studies. The labels for gadolinium-containing contrast agents caution that the risk of toxic reactions may be greater in patients with impaired kidney function because gadolinium is mostly excreted by the kidney.

13. What should patients do with this new information?

If you have severely impaired kidney function and you received a gadolinium contrast MRA, you should bring this to the attention of your treating physician. If you have advanced kidney failure and a physician has prescribed an MRI or MRA study with contrast, ask if there are alternative diagnostic contrast agents or tests that could be as effective.

14. What should healthcare providers do in response to this new information?

    Physicians should be cautious regarding the use of gadolinium-containing contrast agents, especially at high doses, in patients with advanced renal failure. If such a patient receives gadolinium contrast MRA, prompt dialysis should be considered. Physicians should also report all cases of NSF/NSD to the FDA MedWatch at www.fda.gov/medwatch/.

15. What additional actions are likely to follow?

    FDA will complete its ongoing analysis of these preliminary findings and then consider multiple options such as: modifying the product label or requiring additional studies. FDA may also consider risk management options.

16. Where can I find more information about gadolinium-containing agents and about NSF/NFD?

    The package inserts provide more information about all of the approved gadolinium-containing agents. More information about NSF/NFD can be found at the following website: http://www.pathmax.com/dermweb/.